Multicatalysis Protocol Enables Direct and Versatile Enantioselective Reductive Transformations of Secondary Amides

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α-Stereogenic amines are ubiquitous in biologically active natural products, medicinal agents, and agrochemicals (Figure 1). Amides have long been considered as ideal starting materials for the synthesis of functionalized amines, because of their ready availability and high stability. However, the latter property renders the direct conversion of amides into amines challenging, which is particularly true for catalytic asymmetric transformations such as the catalytic, asymmetric reductive alkynylation and reductive alkylation of secondary amides. Indeed, these transformations – according to Professor Pei-Qiang Huang, from Xiamen University (P. R. of China) – remain unconquered.

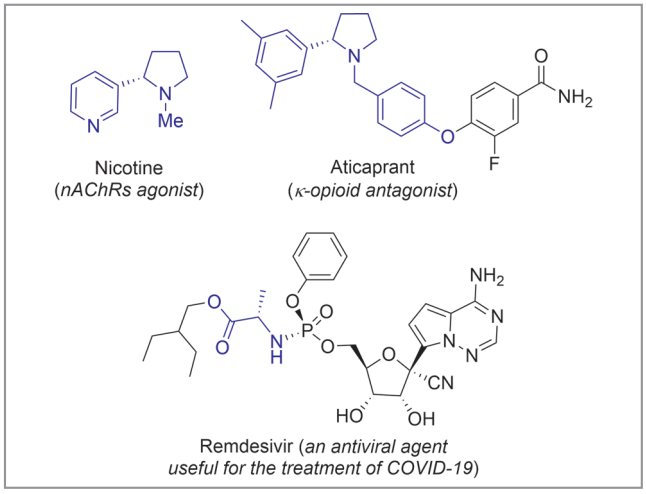
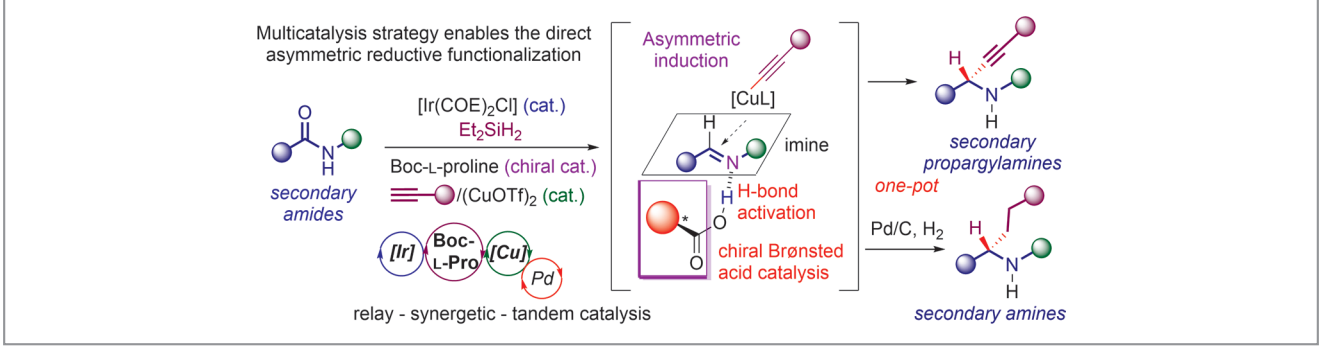


Figure 1 Selected examples of bioactive natural products and medicinal agents featuring an α-chiral amine motif

Professor Huang pointed out to SYNFORM that: "Before addressing the chemistry in the title article, we have engaged in the field of direct transformation of common amides for more than twelve years. In 2010 and 2012, Dr. Kai-Jiong Xiao, one of my former Ph.D. students, developed the first general methods for the reductive bis-alkylation (*Angew. Chem. Int. Ed.* **2010**, *49*, 3037) and reductive mono-alkylation of amides (*tert*-amides: *Chem. Eur. J.* **2010**, *16*, 12792; *sec*-amides: *Angew. Chem. Int. Ed.* **2012**, *51*, 8314) using stoichiometric triflic anhydride as an amide activating agent. In 2016, Dr. Wei Ou, another of my former Ph.D. students, developed the first iridium and copper relay-catalyzed reductive alkynylation of tertiary (*Chem. Commun.* **2016**, *52*, 11967) and secondary amides (*Angew. Chem. Int. Ed.* **2018**, *57*, 11354)." He continued, "After these two steps, it was natural to seek the asymmetric versions of the above-mentioned reactions. In this context, we had obtained some encouraging results (*Org. Lett.* **2019**, *21*, 7587). In particular, we demonstrated recently that the enantioselective reductive cyanation and phosphonylation of secondary amides could be achieved by iridium and chiral thiourea sequential catalysis (*Angew. Chem. Int. Ed.* **2021**, *60*, 8827)."

"Those results inspired me to look for a multi-catalysis system for the enantioselective reductive alkynylation of secondary amides," remarked Dr. Hang Chen, first author of



Scheme 1 The strategy for the direct, catalytic enantioselective deoxygenative alkynylation and alkylation of secondary amides

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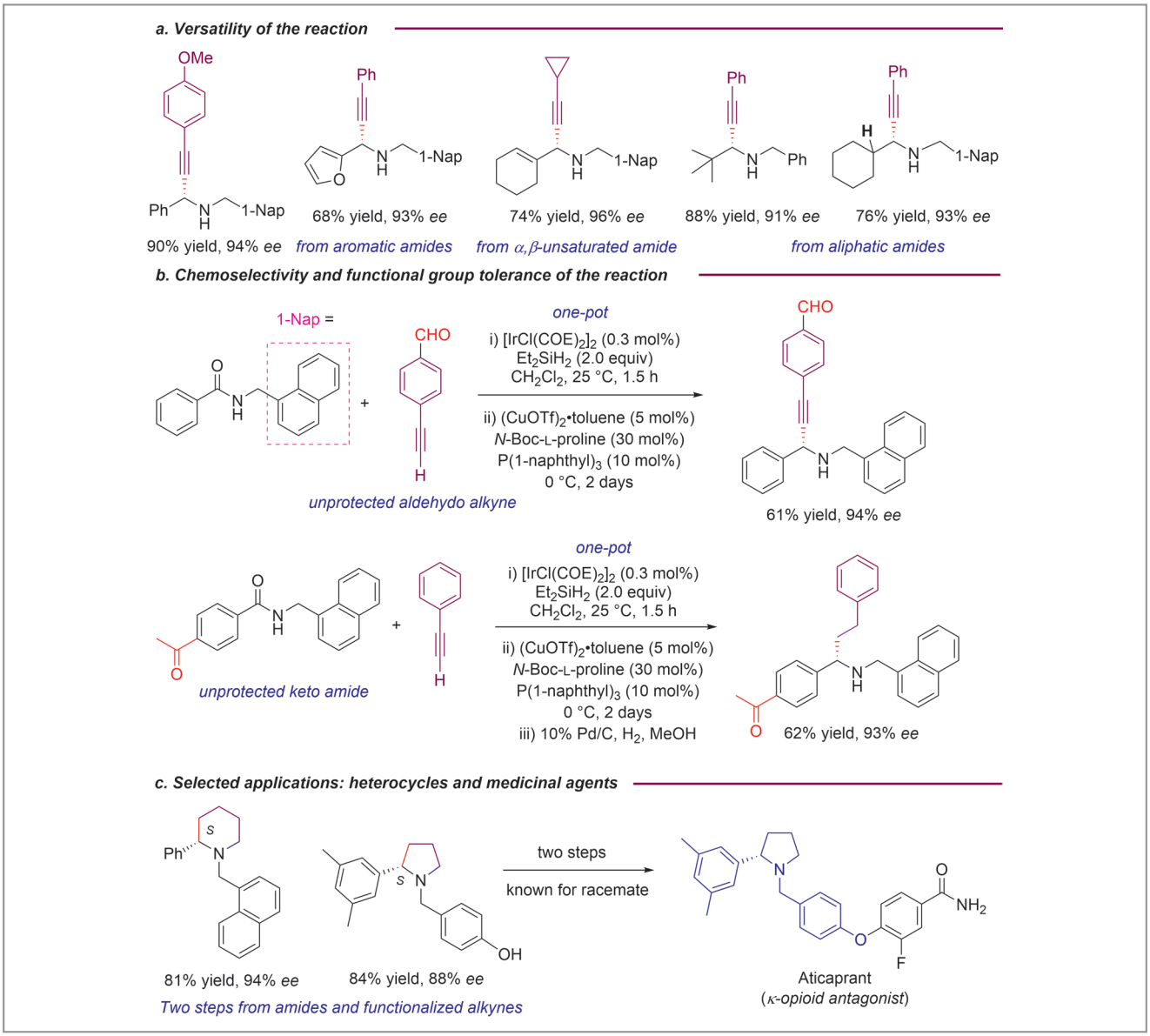
the title article and the Ph.D. student who initiated the project, adding: "The observed significant difference between CuBr and CuOTf in the asymmetric reaction allows us to suggest the asymmetric induction model shown in Scheme 1. Boc-L-proline is an effective Brønsted acid-type organocatalyst to achieve both high enantioselectivity and good yield, which are also influenced by the achiral phosphorus ligands and *N*-protection groups of L-proline."

"The *N*-alkyl group of amides plays an important role in the asymmetric induction," said Zhi-Zhong Wu, Master's student and another first author of the title article. He added: "By further combining the method with Pd/C-catalyzed hydrogenation/hydrogenolysis, we achieved the formal reductive alkylation of secondary amides and thus extended the scope of the reaction, enabling the straightforward catalytic asymmetric synthesis of α-aryl piperidines and α-aryl pyrrolidines, as illustrated by the first asymmetric approach to the medicinal agent aticaprant."

Professor Guo-Qiang Lin at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, an expert of



Scheme 2 Selected examples illustrating the scope and applicability of the method

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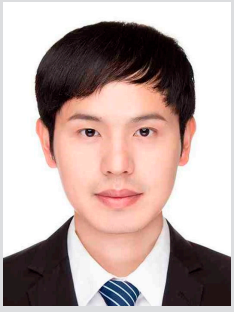
metal catalysis in organic synthesis, commented to SYNFORM that: "The exceptional chemoselectivity and functional group tolerance, allowing the reactions to take place preferentially at the less reactive amide group over the more reactive ester and ketone moieties, and for the use of alkynes bearing ester and unprotected aldehyde groups (Scheme 2) is remarkable, which renders the method promising for applications in the total synthesis of alkaloids and N-containing medicinal agents."

Professor Huang concluded: "Although our method is versatile, the reaction of α-unbranched aliphatic amides gave unsatisfactory results, which prompts us to develop more general methods in the future. It is worth noting that our work was also inspired by recent developments in related fields. We believe that this multi-catalysis strategy will also be applicable to the development of catalytic asymmetric transformations of other carboxylic acid derivatives."

About the authors



Dr. H. Chen

Hang Chen received his B.Sc. from Anhui Normal University and Ph.D. from Xiamen University (P. R. of China), where he worked in the field of methodology development based on the amide transformation under the supervision of Prof. Pei-Qiang Huang and Assoc. Prof. Jian-Liang Ye.

Z-Z Wu

Zhi-Zhong Wu was born in Zhangzhou (P. R. of China) in 1996. He received his Bachelor's (2019) and Master's (2022) degrees from Xiamen University (P. R. of China) under the supervision of Prof. Pei-Qiang Huang, where he worked on catalytic direct transformation of amides.

D-Y Shao

Dong-Yang Shao received his B.Sc. from Wuhan Institute of Technology (P. R. of China). Currently, he is pursuing his Master's degree under the supervision of Prof. Pei-Qiang Huang at Xiamen University (P. R. of China). His current research interests include developing C–C bond formation methods based on amide activation.

Prof. P-Q Huang

Pei-Qiang Huang is a Professor at the College of Chemistry and Chemical Engineering at Xiamen University (P. R. of China). He received his D. E. A. in 1984 from Université de Montpellier II (France) under the direction of Professor B. Castro (INSERM-CNRS). He completed the research work at the Institut de Chimie des Substances Naturelles (ICSN), CNRS under the direction of Professor H.-P. Husson, and received his Ph.D. from the Université de Paris-Sud (Orsay) (France) in 1987. In 1988, he joined Professor W.-S. Zhou's group at the Shanghai Institute of Organic Chemistry (SIOC), CAS (P. R. of China), as a postdoctoral fellow. In 1990, he returned to Xiamen University. The Huang group's research focuses on the development of novel and efficient synthetic methodologies, and the total synthesis of bioactive natural products. He has coauthored several books including 'Efficiency in Natural Product Total Synthesis' (Wiley, 2018) with Z.-J. Yao and R. P. Hsung.

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